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RESEARCH ARTICLE

Effect of dapagliflozin on anaemia in DAPA-HF

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Aim Anaemia is common in heart failure and associated with worse outcomes. We examined the effect of dapagliflozin on correction of anaemia in patients with heart failure (HF) and reduced ejection fraction in DAPA-HF. We also analysed the effect of dapagliflozin on outcomes, according to anaemia status at baseline.

Methods and results Anaemia was defined at baseline as a haematocrit <39% in men and <36% in women. Resolution of anaemia was defined as two consecutive haematocrit measurements above these thresholds at any time during follow-up. The primary outcome was a composite of worsening HF (hospitalization or urgent visit requiring intravenous therapy) or cardiovascular death. Of the 4744 patients randomized in DAPA-HF, 4691 had a haematocrit available at baseline, of which 1032 were anaemic (22.0%). The rate of the primary outcome was higher in patients with anaemia (16.1 per 100 person-years) compared with those without (12.9 per 100 person-years). Anaemia was corrected in 62.2% of patients in the dapagliflozin group, compared with 41.1% of patients in the placebo group. The effect of dapagliflozin on the primary outcome was consistent in anaemic compared with non-anaemic patients [hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.52–0.88 vs. HR 0.76, 95% CI 0.65–0.89; interaction $P = 0.44$]. Similar findings were observed for cardiovascular death, HF hospitalization, and all-cause mortality. Patients with resolution of anaemia had better outcomes than those in which anaemia persisted.

Conclusion Patients with anaemia had worse outcomes in DAPA-HF. Dapagliflozin corrected anaemia more often than placebo and improved outcomes, irrespective of anaemia status at baseline.

Keywords Heart failure with reduced ejection fraction • Anaemia • Clinical trials • Sodium–glucose co-transporter 2 inhibitor

Introduction

Anaemia is a common finding in heart failure although it was not recognized as such until the turn of the century.[1,2] Its aetiology is complex, probably reflecting renal impairment, inflammation, iron deficiency and treatment with angiotensin-converting enzyme inhibitors, among other factors.[1] Patients with anaemia generally have worse symptoms, greater functional impairment, higher rates of hospital admission and shorter survival than those without.[3] Anaemia remains prognostically important, even when other

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predictive variables are accounted for.[4] Why anaemia is an independent predictor of worse outcomes is not fully understood. However, given that heart failure, physiologically, is a syndrome in which oxygen delivery to the metabolizing tissues is insufficient, it is clear why anaemia might be an exacerbating factor.[5] There have been attempts to correct anaemia in heart failure, using different approaches.[6–10] The erythropoiesis-stimulating darbepoetin did not reduce the risk of death or hospitalization for heart failure but did improve quality of life.[6] Several studies have shown that intravenous iron improves symptoms, quality of life and functional capacity.[7–9] The Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency (AFFIRM-AHF) reported that in hospitalized patients stabilized from an episode of worsening heart failure, the administration of intravenous ferric carboxymaltose reduced the risk of rehospitalization for heart failure compared with placebo and ongoing trials will provide further data regarding the long-term effects of intravenous iron on morbidity and mortality in heart failure.[10]

Recently, sodium–glucose co-transporter 2 inhibitors (SGLT2i) have been shown to increase haematocrit.[11–13] While, initially, this was thought simply to reflect volume contraction due to diuresis, there is growing evidence that these drugs may stimulate erythropoiesis by suppressing hepcidin and increasing erythropoietin.[14–18] The placebo-controlled Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF) provides a unique opportunity to examine whether a SGLT2i corrects anaemia in patients with heart failure and reduced ejection fraction (HFrEF) and the impact of this treatment on symptoms, quality of life, hospitalization and mortality.[12]

Methods

DAPA-HF was a prospective, randomized, double-blind, placebo-controlled trial in patients with HFrEF, which evaluated the efficacy and safety of dapagliflozin 10 mg once daily, compared with matching placebo, added to standard care.[12,19,20] Ethics committees at each participating institution approved the protocol, and all patients gave written informed consent.

Study patients

Men and women aged ≥18 years in New York Heart Association (NYHA) functional class II–IV, with a left ventricular ejection fraction ≤40% and a modesty elevated concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, were eligible if, in the view of the investigator, they were optimally treated with pharmacological and device therapy, according to local guidelines. Key exclusion criteria included: symptoms of hypotension or systolic blood pressure <95 mmHg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, type 1 diabetes mellitus, and another condition likely to prevent patient participation in the trial or greatly limit life expectancy. There was no specific exclusion related to anaemia or haemoglobin/haematocrit. Concomitant use of an open-label SGLT2i was prohibited. A full list of exclusion criteria is provided in the design paper.[19]

Measurement of haematocrit, haemoglobin and definition of anaemia

Haematocrit was measured at baseline, as well as 14 days, 2 months and 4 months after randomization, and four monthly thereafter. Haemoglobin was measured at baseline and at end of study but not routinely after randomization. All measurements were performed in a central laboratory. Anaemia was defined at baseline as a haematocrit <39% in men and <36% in women.[21] Correction of anaemia after randomization was defined as two consecutive haematocrit measurements above these thresholds at any time during follow-up. For the purposes of sensitivity analyses examining the association between anaemia and outcomes, anaemia was also defined using sex-specific baseline haemoglobin thresholds (male <130 g/L and female <120 g/L). Other laboratory variables (including creatinine and NT-proBNP) and physiological measurements (weight, blood pressure) were made at baseline and during follow-up.

Trial outcomes

The primary outcome was the composite of an episode of worsening heart failure or cardiovascular death, whichever occurred first. An episode of worsening heart failure was either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for heart failure. The first of the secondary outcomes was the composite of heart failure hospitalization or cardiovascular death. The additional secondary outcomes were: total number of recurrent heart failure hospitalizations (including repeat admissions) and cardiovascular deaths; change from baseline to 8 months in the total symptom score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS) using a scale from 0 to 100, with a higher score indicating fewer symptoms and a ≥5 point change considered clinically meaningful[22]; the incidence of a composite worsening renal function outcome (there were few of these events); and death from any cause. All cardiovascular endpoints and deaths were adjudicated by an independent, blinded, committee.

For the purposes of this analysis, we examined the effect of dapagliflozin, compared to placebo, on the primary composite outcome, the individual components of cardiovascular death and worsening heart failure events (defined as hospitalization for heart failure or an urgent outpatient visit requiring use of intravenous therapy) and the pre-specified secondary endpoints of total events and death from any cause. We also examined the additional effect on KCCQ overall summary score (OSS) and clinical summary score (CSS).

Statistical analysis

Baseline characteristics were compared between anaemia groups by using the two-sample *t*-test and Wilcoxon rank-sum test for normal and non-normal continuous variables and the χ^2 test for categorical variables. The cumulative incidence of the primary endpoint by treatment assignment in the anaemia subgroups was analysed by means of the Kaplan–Meier method and plotted graphically. The effect of dapagliflozin compared to placebo on each outcome was examined by means of hazard ratio (HR) and 95% confidence intervals (CI) derived from Cox proportional-hazards models adjusted for a history of hospitalization for heart failure and treatment assignment and stratified by baseline diabetes status. For the anaemia yes/no subgroup analyses, an interaction test was performed to assess for any modification of treatment effect by anaemia status. The relationship between anaemia at baseline and subsequent outcomes was examined by means examined by means of HR and 95% CI derived from Cox

proportional-hazards models adjusted for a history of hospitalization for heart failure and treatment assignment. For the endpoint of all-cause mortality, no adjustment for a history of hospitalization for heart failure was performed. The effect on the composite endpoint of recurrent (first and total HF hospitalizations) and cardiovascular death was examined using a semiparametric proportional-rates model.[23] A second analysis was performed with further adjustment for age, heart rate, systolic blood pressure, body mass index, ischaemic aetiology of heart failure, left ventricular ejection fraction, NYHA functional classification, NT-proBNP, atrial fibrillation, mineralocorticoid receptor antagonist use and eGFR. The relative hazard of death from any cause and cardiovascular causes following reversal of anaemia was examined in a Cox proportional-hazards model where an indicator of a resolution of anaemia was entered into the model as a time-updated covariate (with follow-up time starting at randomization). The period at risk prior to resolution of anaemia was attributed to the group who had persisting anaemia in order to calculate incidence rates which reflect patients' time-updated event status. The model was repeated with adjustment for randomized treatment, history of heart failure hospitalization, age, sex, heart rate, systolic blood pressure, body mass index, ischaemic aetiology of heart failure, left ventricular ejection fraction, NYHA functional classification, NT-proBNP, atrial fibrillation, and eGFR and diabetes status. This analysis was repeated for the endpoint of recurrent heart failure hospitalizations and cardiovascular death using using a semiparametric proportional-rates model. Changes in vital signs and laboratory values were analysed using a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment and interaction of treatment and visit with a random intercept and slope per patient) and the between-treatment group difference at 8 months following randomization are presented by subgroup as least square means difference and 95% CI. In patients randomized to dapagliflozin, the correlation between change in haematocrit and other laboratory measures and vital signs at visit 3 (14 days) and visit 6 (8 months) was examined using Pearson's correlation coefficient. The effect of dapagliflozin on the reversal or development of anaemia during follow-up was examined with a logistic regression model with randomized treatment as the only independent variable. A sensitivity analysis was performed using a mixed-effects logistic regression model with correction of anaemia occurring at any time during follow-up defined using the haematocrit thresholds detailed previously. The treatment effect on the proportion of patients with a clinically meaningful improvement (≥5 point increase) or deterioration (≥5 point decrease) in KCCQ scores is presented as an odds ratios (OR) with 95% CI calculated using methods described previously.[22] All analyses were performed using Stata version 16 (Stata Corp., College Station, TX, USA) and SAS, version 9.4 (SAS Institute, Cary, NC, USA). A *P*-value <0.05 was considered statistically significant.

Results

Of the 4744 patients randomized in DAPA-HF, 4691 had a haematocrit available at baseline and 1032 of these participants were anaemic (22.0%). The distribution of baseline haematocrit and haemoglobin by sex is shown in online supplementary *Figure S1*. The proportion of patients with anaemia in the dapagliflozin and placebo groups did not differ significantly [535/2346 (22.8%) vs. 497/2345 (21.2%)]. In a sensitivity analysis, using sex-specific baseline haemoglobin thresholds (male <130 g/L and female <120 g/L), the proportion of patients with anaemia was 27.7% and this was also balanced across the two treatment groups.

Patient characteristics according to anaemia status at baseline

The baseline characteristics of patients according to their anaemia status are shown in *Table 1*. Compared to those who were not anaemic, patients who were anaemic were older, more likely to be male and had a lower mean systolic blood pressure, higher NT-proBNP level, and worse kidney function. A history of coronary heart disease, diabetes and prior heart failure hospitalization was more common among patients with anaemia, compared to those without anaemia. NYHA functional class and KCCQ-TSS did not differ significantly between those with and without anaemia. The prescription of key treatments was similar in the two groups, except for use of a mineralocorticoid receptor antagonist, which was less in individuals with anaemia. During follow-up, a small number of patients received treatments for iron deficiency and/or anaemia (including patients taking these at the time of randomization); intravenous iron in 12 (0.5%) and 13 (0.5%), oral iron in 123 (5.2%) and 117 (4.9%), vitamin B12 in 72 (3.0%) and 71 (3.0%), and folic acid in 51 (2.1%) and 56 (2.4%) patients randomised to dapagliflozin and placebo, respectively.

Cardiovascular outcomes according to anaemia status at baseline

The cumulative incidence of the primary composite endpoint and the secondary morbidity/mortality endpoints are shown in *Figure 1* and *Table 2*. For each of these, the risk was higher in individuals with anaemia than in those without, in unadjusted analyses. After adjustment, only worsening heart failure and not death remained significantly higher in anaemic patients. In a sensitivity analysis using a haemoglobin-based definition of anaemia, in adjusted analyses anaemia was associated with a significantly higher risk of the primary composite endpoint, worsening heart failure, all-cause mortality and the composite endpoint of total heart failure hospitalizations and cardiovascular death (online supplementary *Table S1*).

Effects of dapagliflozin on haematocrit and anaemia status after randomization

Change in haematocrit from baseline is shown in *Figure 2*. The time course and magnitude of the change with dapagliflozin was similar in patients with and without anaemia. The mean placebo-corrected increase at 8 months was 2.38 (1.93 to 2.83)% in participants with anaemia and 2.44 (2.21 to 2.67)% in those without anaemia (interaction $P = 0.88$) (*Table 3*). The proportion of patients who were anaemic at baseline and experienced a persistent rise in haematocrit into the non-anaemic range was 62.2% in the dapagliflozin group and 41.1% in the placebo group, giving an OR for anaemia correction of 2.37 (95% CI 1.84–3.04; $P < 0.001$). A similar result was seen in a sensitivity analysis using a mixed-effects logistic regression model (OR 3.06, 95% CI 1.95–4.80; $P < 0.001$). In a further sensitivity analysis in patients who were anaemic at baseline according to standard sex-specific haemoglobin thresholds, using the last recorded haemoglobin measurement during follow-up the OR for dapagliflozin vs. placebo for correction of anaemia was

Table 1 Baseline characteristics by presence of anaemia

	No anaemia ($n = 3659$)	Anaemia ($n = 1032$)	*P*-value
Age, years	65.4 ± 11.0	69.8 ± 9.7	<0.001
Sex			<0.001
Female	893 (24.4)	200 (19.4)	
Male	2766 (75.6)	832 (80.6)	
Race[a]			<0.001
White	2623 (71.7)	673 (65.2)	
Asian	826 (22.6)	284 (27.5)	
Black	153 (4.2)	63 (6.1)	
Other	57 (1.6)	12 (1.2)	
Region			<0.001
Asia/Pacific	826 (22.6)	284 (27.5)	
Europe	1745 (47.7)	408 (39.5)	
North America	444 (12.1)	227 (22.0)	
South America	654 (17.9)	121 (11.7)	
NYHA functional class			0.13
II	2440 (66.7)	718 (69.6)	
III	1182 (32.3)	308 (29.8)	
IV	37 (1.0)	6 (0.6)	
Heart rate, bpm	71.7 ± 11.7	70.6 ± 11.4	0.008
Systolic blood pressure, mmHg	122.3 ± 16.2	120.2 ± 16.5	<0.001
Left ventricular ejection fraction, %	31.0 ± 6.9	31.5 ± 6.6	0.036
NT-proBNP, pg/mL	1350.9 [820.5–2442.2]	1840.0 [1042.8–3314.9]	<0.001
KCCQ-TSS	77.1 [58.3–91.7]	78.1 [60.4–91.7]	0.39
Haemoglobin (g/L)	140.6 ± 13.4	117.7 ± 12.2	<0.001
Body mass index, kg/m^2	28.4 ± 6.0	27.2 ± 5.9	<0.001
Principal cause of heart failure			0.033
Ischaemic	2031 (55.5)	619 (60.0)	
Non-ischaemic	1331 (36.4)	333 (32.3)	
Unknown	297 (8.1)	80 (7.8)	
Medical history			
Hospitalization for heart failure	1702 (46.5)	510 (49.4)	0.099
Atrial fibrillation	1408 (38.5)	391 (37.9)	0.73
Type 2 diabetes[b]	1433 (39.2)	526 (51.0)	<0.001
Prior MI	1598 (43.7)	476 (46.1)	0.16
Prior PCI	1229 (33.6)	384 (37.2)	0.031
Prior CABG	559 (15.3)	231 (22.4)	<0.001
eGFR, mL/min/1.73 m^2	67.6 ± 19.2	59.3 ± 18.6	<0.001
eGFR rate <60 mL/min/1.73 m^2	1355 (37.0)	550 (53.3)	<0.001
Device therapy			
Implantable cardioverter-defibrillator[c]	945 (25.8)	285 (27.6)	0.25
Cardiac resynchronization therapy[d]	263 (7.2)	90 (8.7)	0.099
Heart failure medication at randomization visit			
Diuretic	3070 (83.9)	893 (86.5)	0.039
ACE-inhibitor or ARB	3072 (84.0)	829 (80.3)	0.006
Sacubitril/valsartan	385 (10.5)	123 (11.9)	0.20
Beta-blocker	3519 (96.2)	989 (95.8)	0.62
MRA	2653 (72.5)	687 (66.6)	<0.001
Digitalis	706 (19.3)	158 (15.3)	0.004
Antiplatelet	1947 (53.2)	610 (59.1)	<0.001
Anticoagulant	1531 (41.8)	416 (40.3)	0.38

Data presented as mean (standard deviation), *n* (%), or median [interquartile range].

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score - range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of ≥75 is considered to reflect satisfactory health status; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

[a]Percentages may not total 100 because of rounding.

[b]993 patients (41.8%) in the dapagliflozin group and 990 in the placebo group (41.8%) had a history of diabetes at baseline. An additional 82 patients in the dapagliflozin group and 74 in the placebo group had previously undiagnosed diabetes defined as a glycated haemoglobin level of ≥6.5% (≥48 mmol/mol) measured in a central laboratory at both screening and randomization.

[c]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.

[d]Cardiac resynchronization therapy with or without a defibrillator.

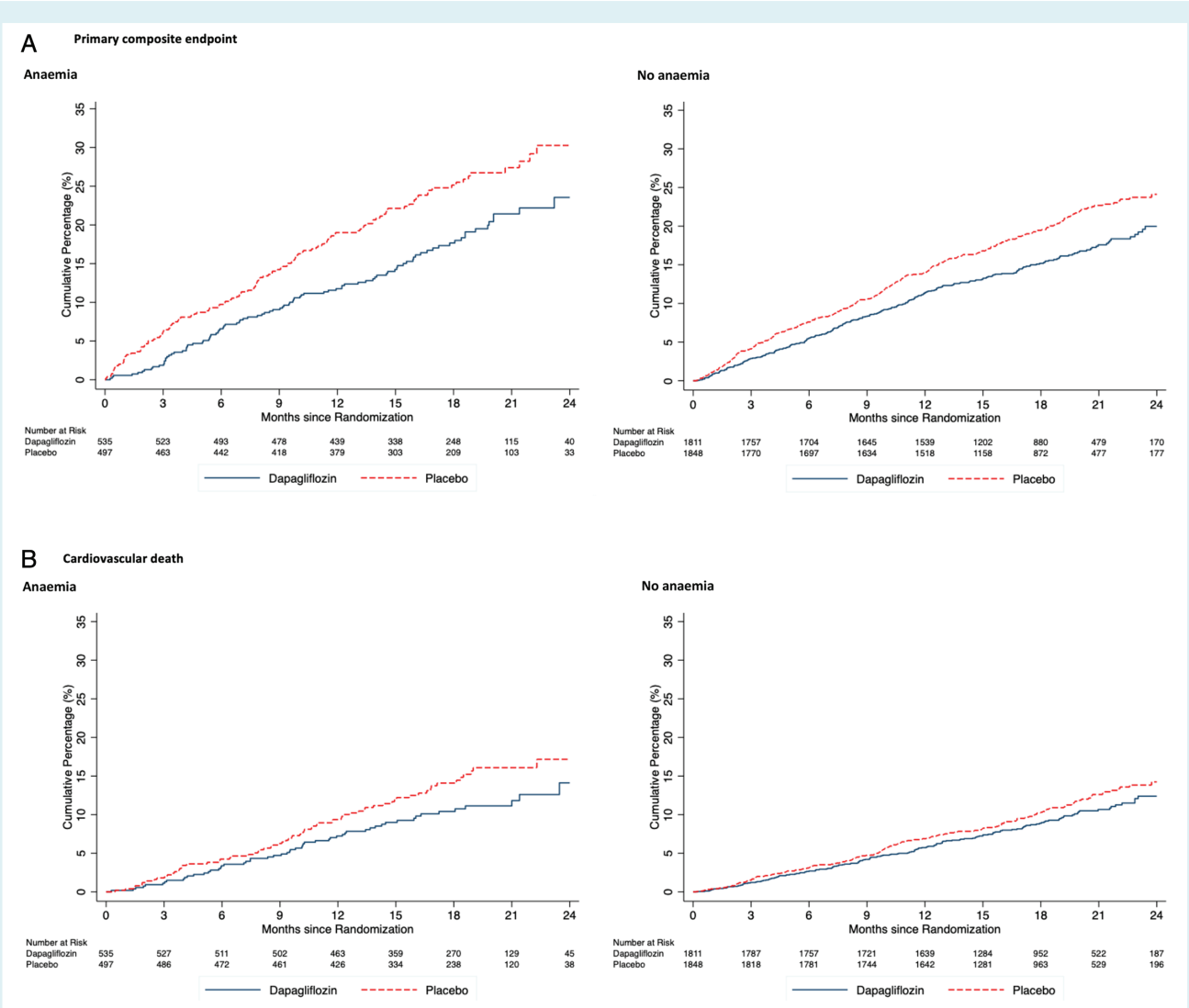

Figure 1 Effect of dapagliflozin compared with placebo on cardiovascular outcomes according to presence of anaemia. Kaplan–Meier estimates of the cumulative incidence of: (*A*) primary composite endpoint [time to first worsening heart failure event, defined as a worsening heart failure event (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes]; (*B*) cardiovascular death; (*C*) worsening heart failure event; (*D*) all-cause mortality.

2.09 (95% CI 1.61–2.71; $P < 0.001$). Conversely, the proportion of patients who were not anaemic at baseline and experienced a decrease in haematocrit into the anaemic range that persisted was 4.5% in the dapagliflozin group and 11.0% in the placebo group, giving an OR for development of anaemia of 0.38 (95% CI 0.29–0.49; $P < 0.001$).

Changes in weight, sodium, urea (blood urea nitrogen), creatinine, urea-to-creatinine ratio, blood pressure, and NT-proBNP from baseline are shown in *Table 3*. The magnitude of these changes was similar in patients with and without anaemia at baseline. At visit 3 (14 days after randomization), there were significant correlations ($P < 0.001$ for all) between change in weight, eGFR, creatinine and urea, and change in haematocrit in patients randomized to dapagliflozin, but all correlations were weak with r values between −0.18 and +0.12 (online supplementary *Table S2*). However, at 8 months, no laboratory or physiological variable correlated significantly with haematocrit.

Effects of dapagliflozin on cardiovascular outcomes according to baseline anaemia status

The effects of dapagliflozin, compared with placebo, in patients with and without anaemia, are shown in *Figure 1* and *Table 4*.

The beneficial effect of dapagliflozin, compared with placebo, on the primary endpoint (HR 0.74, 95% CI 0.65–0.85 in overall trial) was consistent in patients with (HR 0.68, 95% CI 0.52–0.88) and without (HR 0.76, 95% CI 0.65–0.89) anaemia (interaction $P = 0.44$). This beneficial effect was consistent across the range of haematocrit and haemoglobin levels at baseline when examined as a

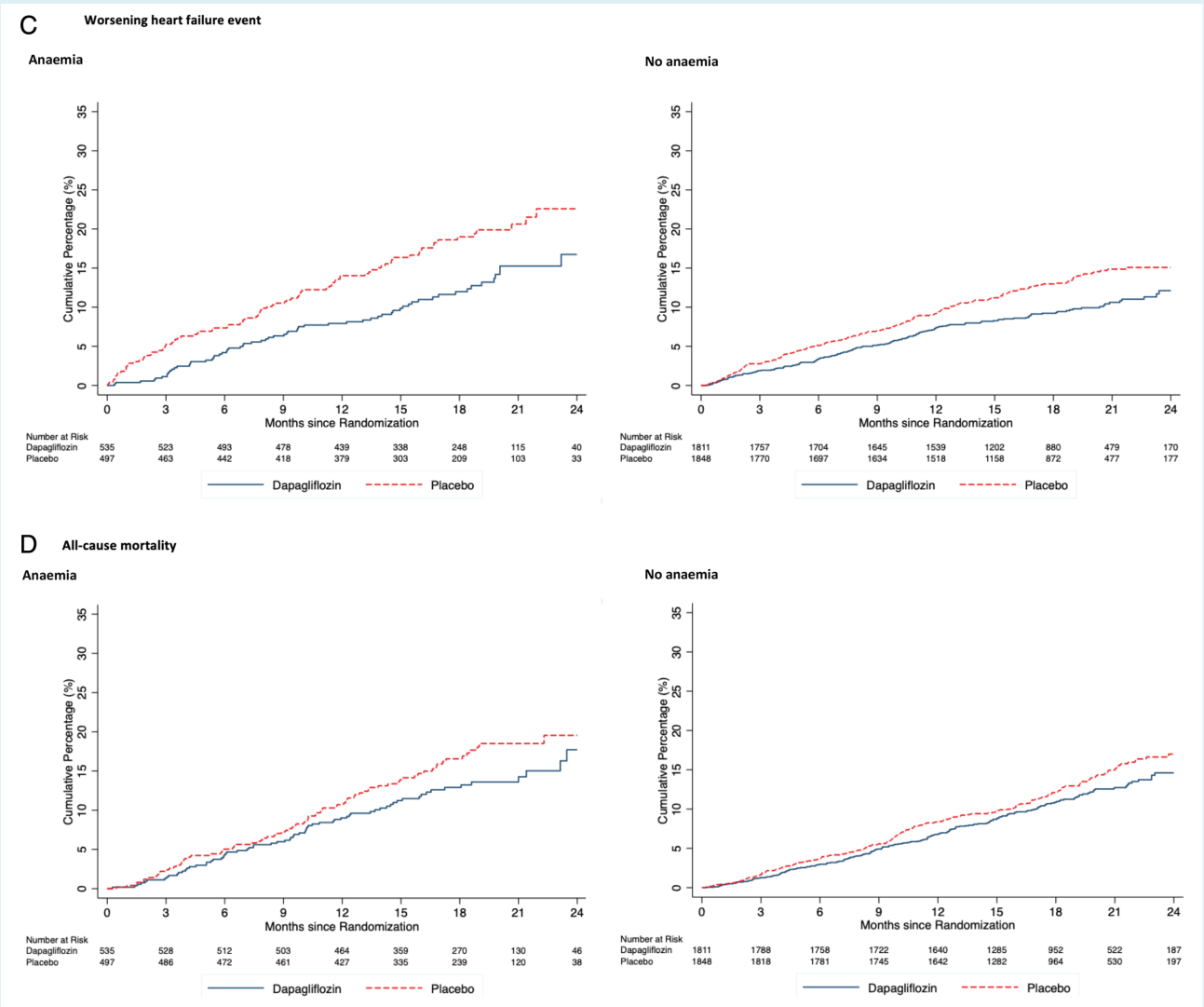

Figure 1 Continued

continuous variable (online supplementary *Figure S2*). In those with anaemia at baseline, there was no modification of the treatment effect of dapagliflozin on the primary endpoint whether patients had resolution (HR 0.73, 95% CI 0.46–1.14) or persistence (HR 0.84, 95% CI 0.60–1.18) of anaemia (interaction $P = 0.66$).

In general, the effect of dapagliflozin on each of the components of the primary outcome and the secondary outcomes was similar both for individuals with and without anaemia (*Figure 1* and *Table 4*).

Because of the much higher event rate in anaemic patients, the absolute risk reductions with dapagliflozin, compared with placebo, were larger than in non-anaemic patients, i.e. 6.2 vs. 3.5 per 100 person-years for the primary composite outcome, 2.6 vs. 1.1 per 100 person-years for cardiovascular death and 5.1 vs. 2.5 per 100 person-years for worsening heart failure.

Eight months after randomization, the mean increase (improvement) in KCCQ-TSS with dapagliflozin, compared with placebo, was greater in patients with anaemia (+4.3, 95% CI 1.7–7.0) compared to those without (+2.5, 95% CI 1.1–3.8), although this difference between anaemic and non-anaemic patient subgroups was not statistically significant (interaction $P = 0.34$) (*Table 5*). A similar picture was seen for KCCQ-CSS and KCCQ-OSS.

Outcomes associated with resolution vs. persistence of anaemia during follow-up

When resolution of anaemia was considered a time-updated covariate, the rate of the composite outcome of total (including recurrent) heart failure hospitalizations and cardiovascular death in patients with anaemia at baseline who had resolution of anaemia ($n = 537$, 52%), irrespective of treatment allocation, was lower than in those who had persistence of anaemia during follow-up ($n = 495$, 48%): 19.7 (95% CI 16.2–23.9) per 100 person-years vs. 27.7 (95% CI 24.5–31.3) per 100 person-years, giving an adjusted HR of this outcome for resolution vs. persistence of anaemia of 0.75 (95% CI

Table 2 Outcomes according to anaemia status defined using haematocrit thresholds

Outcome	Event rate per 100 person-years		Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	Anaemia ($n = 1032$)	No anaemia ($n = 3659$)		
Primary composite endpoint	16.1 (14.1–18.4)	12.9 (11.9–13.9)	1.20 (1.03–1.40); $P = 0.020$	1.06 (0.91–1.25); $P = 0.45$
Cardiovascular death	8.7 (7.3–10.3)	6.9 (6.2–7.6)	1.23 (1.00–1.50); $P = 0.047$	0.99 (0.80–1.23); $P = 0.94$
Worsening HF event	11.3 (9.6–13.2)	7.9 (7.1–8.7)	1.35 (1.12–1.63); $P = 0.002$	1.22 (1.00–1.48); $P = 0.046$
All-cause mortality	10.4 (8.9–12.2)	8.3 (7.6–9.1)	1.23 (1.02–1.48); $P = 0.030$	0.99 (0.82–1.20); $P = 0.93$
Total HF hospitalizations and cardiovascular death[a]	24.5 (22.1–27.2)	17.5 (16.4–18.6)	1.34 (1.13–1.59); $P = 0.001$	1.14 (0.96–1.36); $P = 0.14$

CI, confidence interval; HF, heart failure; HR, hazard ratio.
HR presented as anaemia vs. no anaemia.
Unadjusted analysis includes factors for randomized treatment and history of HF hospitalization and is stratified by diabetes status.
Adjusted analysis includes factors for randomized treatment, history of HF hospitalization, age, heart rate, systolic blood pressure, body mass index, ischaemic aetiology of HF, left ventricular ejection fraction, NYHA functional class, N-terminal pro-B-type natriuretic peptide, atrial fibrillation, mineralocorticoid receptor antagonist use and estimated glomerular filtration rate.
[a]Risk estimate presented as rate ratio.

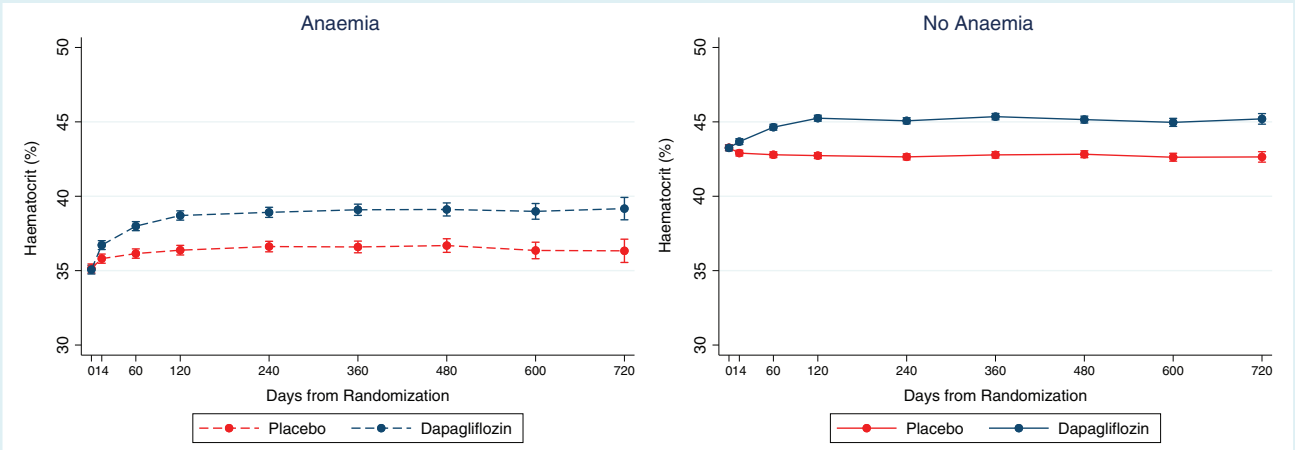

Figure 2 Effect of dapagliflozin compared with placebo on haematocrit according to presence of anaemia. Least square means and 95% confidence intervals were derived from a mixed-effects model adjusted for baseline values, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient.

0.58–0.97) (online supplementary *Table S3*). The risk of both cardiovascular death and death from any cause was lower in those with resolution of anaemia in unadjusted analyses; however, this was not statistically significant after adjustment for other baseline variables (online supplementary *Table S3*). Conversely, the development of anaemia was associated with an approximately twofold increased unadjusted risk of both death from any cause (HR 2.40, 95% CI 1.76–3.28) and the composite endpoint of total (including recurrent) heart failure hospitalizations and cardiovascular death (rate ratio 2.02, 95% CI 1.50–2.72).

Adverse events according to baseline anaemia status

Adverse events and study drug discontinuation were more common in patients with anaemia at baseline (comparing the respective placebo groups) but the rates were not different between dapagliflozin and placebo in either subgroup (online supplementary *Table S4*). The rate of stroke did not differ significantly between treatment arms in the overall DAPA-HF population and there was no significant interaction between baseline anaemia status and randomized treatment on the occurrence of stroke (interaction $P = 0.16$).

Discussion

In this *post-hoc* analysis of DAPA-HF we found that anaemia was common and was associated with worse outcomes, especially if persistent. Resolution of anaemia was more common with dapagliflozin than with placebo, and patients who had resolution of anaemia had better outcomes than those in whom anaemia persisted. The relative risk reductions in the primary and secondary

Table 3 Change in vital signs and laboratory values at 8 months by baseline anaemia status

	Anaemia ($n = 1032$)			No anaemia ($n = 3659$)			Interaction *P*-value
	Dapagliflozin	Placebo	Dapagliflozin vs. placebo	Dapagliflozin	Placebo	Dapagliflozin vs. placebo	
Haematocrit (%)	3.85 (3.54 to 4.16)	1.47 (1.15 to 1.79)	2.38 (1.93 to 2.83)	1.82 (1.66 to 1.99)	−0.62 (−0.78 to −0.45)	2.44 (2.21 to 2.67)	0.88
Sodium (mmol/L)	0.94 (0.67 to 1.21)	0.68 (0.41 to 0.96)	0.26 (−0.13 to 0.64)	1.05 (0.90 to 1.19)	0.72 (0.57 to 0.86)	0.33 (0.13 to 0.53)	0.03
Urea (mg/dL)	0.57 (−0.30 to 1.44)	1.00 (0.10 to 1.90)	−0.43 (−1.68 to 0.83)	0.61 (0.25 to 0.97)	−0.03 (−0.39 to 0.33)	0.64 (0.13 to 1.15)	0.29
Creatinine (mg/dL)	0.09 (0.07 to 0.12)	0.09 (0.06 to 0.12)	0.00 (−0.04 to 0.04)	0.06 (0.05 to 0.07)	0.03 (0.02 to 0.04)	0.03 (0.01 to 0.04)	0.59
Urea-to-creatinine ratio	−0.80 (−1.24 to −0.36)	−0.55 (−1.00 to −0.09)	−0.25 (−0.88 to 0.38)	−0.45 (−0.67 to −0.22)	−0.62 (−0.85 to −0.40)	0.18 (−0.14 to 0.50)	0.10
NT-proBNP (pg/mL)	−173.3 (−442.1 to 95.5)	156.9 (−124.1 to 437.9)	−330.2 (−719.1 to −58.8)	−204.5 (−320.8 to −88.1)	103.3 (−13.0 to 219.6)	−307.8 (−472.3 to −143.2)	0.86
Weight (kg)	−1.14 (−1.46 to-0.82)	−0.18 (−0.51 to 0.15)	−0.95 (−1.41 to −0.49)	−0.78 (−0.95 to −0.61)	0.10 (−0.06 to 0.27)	−0.88 (−1.12 to −0.65)	0.67
Systolic blood pressure (mmHg)	−1.22 (−2.54 to 0.10)	−0.41 (−1.79 to 0.96)	−0.80 (−2.71 to 1.10)	−2.11 (−2.77 to −1.44)	−0.43 (−1.09 to 0.23)	−1.68 (−2.61 to −0.74)	0.34

Means and 95% confidence intervals were derived from a mixed-effects model adjusted for baseline values, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient. Least square mean changes along with 95% confidence intervals are shown.
Interaction *P*-values represent an interaction test between anaemia status at baseline and randomized treatment.

morbidity and mortality endpoints with dapagliflozin, compared with placebo, were consistent in patients with and without baseline anaemia. The absolute risk reductions with dapagliflozin in anaemic individuals were substantial, as a result of the high rates of death and hospitalization in these patients.

In keeping with prior studies in ambulatory patients, just under a quarter of patients in DAPA-HF had anaemia.[4] These participants had additional predictors of poor outcome, including older age, more coronary heart disease and diabetes, lower eGFR and higher NT-proBNP. Consequently, it was not surprising that anaemic patients experienced higher rates of death and hospitalization, as has been documented in many previous reports.[4] More novel was our finding that there was a high rate of anaemia reversal over time (around 40% in the placebo group) and that the risk of adverse outcomes associated with persistence of anaemia was very high, with a more than twofold higher risk of the key death and hospitalization outcomes examined, compared with patients exhibiting reversal of anaemia. Together these findings show that in many patients with HFrEF anaemia is transient and reversible but that when it persists it is associated with much poorer outcomes (the relatively higher risk associated with persisting post-baseline anaemia, compared to baseline anaemia which resolved, was notable). This finding is in keeping with those of Tang and colleagues in a study of 6159 consecutive outpatients with chronic stable heart failure under the care of the Cleveland Clinic.[3]

As anticipated, dapagliflozin increased the rate of anaemia correction (from around 40% to over 60%) and reduced the risk of development of new anaemia by more than half, although the mean increase in haematocrit (around 2.4%) was almost identical in patients with and without anaemia at baseline, demonstrating that many patients had mild anaemia and a 'borderline' baseline haematocrit.

Dapagliflozin was beneficial in patients without anaemia as well as in those with anaemia at baseline, although the absolute risk reductions in hospitalization and death with dapagliflozin were greater in anaemic individuals, given their higher baseline risk of these outcomes. There was an absolute reduction of over 7% in the primary composite endpoint in anaemic patients treated with dapagliflozin for a median of 18.2 months. Consequently, while dapagliflozin has large and worthwhile benefits in a broad range of patients with HFrEF, it may be a particularly useful therapy for individuals with anaemia because it can correct anaemia, as well as substantially reduce the elevated risk such patients face.

The much more difficult question to answer is whether correction of anaemia contributed to the improvement in outcomes with dapagliflozin. In several modest-sized, short-term, trials, intravenous iron increased haematocrit and haemoglobin and improved symptoms, health-related quality of life and functional capacity.[7–9] The AFFIRM-AHF trial recently reported a reduction in the risk of heart failure hospitalization with intravenous iron replacement with no significant effect on cardiovascular death.[10] Further ongoing trials will provide more data regarding the effect of this therapeutic approach. Conversely, while the larger, longer-term, Reduction of Events With Darbepoetin Alfa in Heart Failure trial (RED-HF) showed anaemia correction with a synthetic

Table 4 Effect of dapagliflozin compared with placebo on cardiovascular outcomes according to anaemia status

	Dapagliflozin		Placebo		Hazard ratio (95% CI)	Interaction *P*-value
	n/N (%)	Rate per 100 person-years (95% CI)	*n*/N (%)	Rate per 100 person-years (95% CI)		
Primary composite endpoint						
Anaemia ($n = 1032$)	97/535 (18.1)	13.2 (10.9–16.2)	125/497 (25.2)	19.4 (16.3–23.1)	0.68 (0.52–0.88)	0.44
No anaemia ($n = 3659$)	285/1811 (15.7)	11.1 (9.9–12.5)	371/1848 (20.1)	14.6 (13.2–16.2)	0.76 (0.65–0.89)	
Cardiovascular death						
Anaemia ($n = 1032$)	57/535 (10.7)	7.4 (5.7–9.6)	70/497 (14.1)	10.0 (7.9–12.6)	0.74 (0.52–1.05)	0.48
No anaemia ($n = 3659$)	169/1811 (9.3)	6.3 (5.4–7.3)	201/1848 (10.9)	7.4 (6.5–8.5)	0.85 (0.70–1.05)	
Worsening HF event						
Anaemia ($n = 1032$)	65/535 (12.1)	8.9 (7.0–11.3)	90/497 (18.1)	14.0 (11.4–17.2)	0.63 (0.46–0.86)	0.48
No anaemia ($n = 3659$)	169/1811 (9.3)	6.6 (5.7–7.7)	232/1848 (12.6)	9.1 (8.0–10.4)	0.72 (0.59–0.88)	
All-cause mortality						
Anaemia ($n = 1032$)	71/535 (13.3)	9.3 (7.3–11.7)	82/497 (16.5)	11.7 (9.4–14.5)	0.78 (0.57–1.08)	0.67
No anaemia ($n = 3659$)	204/1811 (11.3)	7.6 (6.6–8.7)	244/1848 (13.2)	9.0 (7.9–10.2)	0.85 (0.70–1.02)	
Total HF hospitalizations and cardiovascular death[a]						
Anaemia ($n = 1032$)	151[b]	19.8 (16.9–23.2)	206[b]	29.7 (25.9–34.0)	0.66 (0.49–0.89)	0.30
No anaemia ($n = 3659$)	412[b]	15.4 (14.0–17.0)	526[b]	19.5 (17.9–21.2)	0.79 (0.67–0.94)	

CI, confidence interval; HF, heart failure.
[a]Risk estimate presented as rate ratio.
[b]Number of events.

erythropoiesis-stimulating agent and improved health-related quality of life, it did not show a reduction in mortality or morbidity.[6] Consequently, to date, there is no other evidence supporting a contribution of anaemia correction to the reduction in hospitalization and death seen with dapagliflozin, although that possibility is not precluded either, and the means of anaemia correction may be an important consideration.

Irrespective of the uncertainty about the effect of anaemia correction on hospitalization and death, treating anaemia does improve health-related quality of life, and diminished oxygen carrying capacity of the blood, limiting the delivery to meet the metabolic demands of the tissues, is unfavourable in heart failure. A safe means of correcting anaemia is therefore valuable in HFrEF. As discussed earlier, the increase in haematocrit observed with SGLT2i is no longer believed to simply reflect volume contraction due to diuresis. Several lines of evidence argue against volume contraction being the only or even main explanation. Firstly, the assumption that diuresis increases haematocrit in patients with heart failure has little support from studies in patients with heart failure given usual oral doses of conventional diuretics.[15,24,25] Second, the evidence that SGLT2i have a diuretic and natriuretic action in heart failure is conflicting and any effect seems to be small and short-lived.[26–28] Moreover, SGLT2i seem to remove interstitial rather than intravascular fluid.[29] Thirdly, as we have reported elsewhere, the increase in haematocrit with dapagliflozin was similar in patients taking or not taking a conventional diuretic and in patients on larger and smaller doses of diuretic; adding another diuretic would likely have causes different from changes in volume status in these various groups.[30] The change in haematocrit is also similar in patients with and without diabetes and with and without chronic kidney disease, whereas the glucosuric and diuretic effect of SGLT2i is different in these different clinical situations.[11,31,32] In support of this, we saw no change in urea after initiation of dapagliflozin; the rise in creatinine observed is believed to represent a glomerular haemodynamic action of SGLT2i rather than volume contraction.[33] Furthermore, we observed only weak correlations between these, as well as weight (another potential marker of volume status) and haematocrit early after randomization (14 days) when any diuretic effect of dapagliflozin would be greatest, with no evidence of any correlation at 8 months (with haematocrit continuing to rise from day 14 to a plateau at 8 months).

Conversely, SGLT2i stimulate erythropoiesis by suppressing hepcidin and increasing erythropoietin, although the small physiological changes in the latter are quite distinct from the administration of high-dose exogenous erythropoiesis-stimulating agent as in RED-HF.[6,14–18] A rise in reticulocyte count preceding the rise in haematocrit supports true augmentation of haematopoiesis.[15] An increase in endogenous erythropoietin production is an attractive potential mechanism of action in HFrEF as blunted erythropoietin production has been identified as a contributor to anaemia in heart failure.[4] Clearly, erythropoietin stimulated haematopoiesis raises questions about iron sufficiency, given the high prevalence of iron deficiency in HFrEF, and in one study increased erythropoietin production in response to SGLT2i was associated with a decrease in serum ferritin levels.[34] These observations suggest that further investigation of the effects of SGLT2i on iron utilization and other factors involved in erythropoiesis is warranted in anaemic HFrEF patients.[4,7–10] The potential limitation of erythropoietic response in such patients without concomitant iron replenishment also raises the potential for a therapeutic synergy

Table 5 Effect of dapagliflozin compared with placebo on Kansas City Cardiomyopathy Questionnaire scores at 8 months following randomization according to anaemia status

	Anaemia ($n = 1032$)			No anaemia ($n = 3659$)			Interaction *P*-value
	Dapagliflozin	Placebo	Dapagliflozin vs. placebo	Dapagliflozin	Placebo	Dapagliflozin vs. placebo	
KCCQ-TSS							
Mean change in score at 8 months (95% CI)	+6.5 (4.6–8.4)	+2.2 (0.4–4.0)	+4.3 (1.7–7.0)	+6.0 (5.1–6.9)	+3.6 (2.6–4.6)	+2.5 (1.1–3.8)	0.34
Patients with ≥5 point improvement at 8 months	58.8% (54.2–63.3)	51.0% (46.4–55.7)	1.16 (1.02–1.32)[a]	58.0% (55.6–60.4)	50.8% (48.5–53.1)	1.15 (1.07–1.23)[a]	0.95
Patients with ≥5 point deterioration at 8 months	26.8% (22.8–30.8)	33.6% (29.2–38.0)	0.86 (0.74–0.99)[a]	24.9% (22.8–27.1)	32.7% (30.5–35.0)	0.83 (0.77–0.90)[a]	0.67
KCCQ-CSS							
Mean change in score at 8 months (95% CI)	+5.3 (3.5–7.1)	+1.9 (0.3–3.6)	+3.4 (0.9–5.8)	+5.6 (4.7–6.4)	+3.2 (2.2–4.1)	+2.4 (1.2–3.7)	0.64
Patients with ≥5 point improvement at 8 months	51.0% (46.5–55.5)	41.7% (36.9–46.4)	1.20 (1.04–1.37)[a]	53.9% (51.4–56.3)	45.6% (43.1–48.1)	1.17 (1.09–1.27)[a]	0.82
Patients with ≥5 point deterioration at 8 months	28.0% (24.0–32.0)	32.3% (27.9–36.8)	0.91 (0.79–1.05)[a]	24.5% (22.4–26.6)	31.2% (29.0–33.4)	0.85 (0.79–0.92)[a]	0.41
KCCQ-OSS							
Mean change in score at 8 months (95% CI)	+5.9 (4.2–7.7)	+2.8 (1.2–4.4)	+3.1 (0.8–5.5)	+6.3 (5.5–7.1)	+4.2 (3.3–5.1)	+2.1 (0.9–3.4)	0.54
Patients with ≥5 point improvement at 8 months	50.7% (45.9–55.6)	45.7% (41.2–50.2)	1.09 (0.96–1.25)[a]	54.1% (51.6–56.5)	46.8% (44.3–49.3)	1.15 (1.07–1.23)[a]	0.51
Patients with ≥5 point deterioration at 8 months	28.2% (24.2–32.4)	32.9% (28.4–37.3)	0.90 (0.78–1.04)[a]	23.3% (21.3–25.3)	30.4% (28.2–32.7)	0.84 (0.77–0.90)[a]	0.35

CI, confidence interval; CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; TSS, total symptom score.
[a]Data are presented as odds ratio (95% CI).

between intravenous iron and SGLT2 inhibition in some patients with HFrEF and highlights one potential explanation for why some patients in the present trial did not have correction of anaemia with dapagliflozin.

Finally, it is worth noting that the increase in haematocrit and haemoglobin with SGLT2 inhibition contrasts with the decrease caused by renin–angiotensin system blockers, especially angiotensin-converting enzyme inhibitors and carvedilol.[1,35]

Limitations

As with all studies of this nature there are inherent limitations. Analysis of anaemia was not pre-specified. Erythropoietin, hepcidin, ferritin, red cell mass and reticulocyte count were not measured in DAPA-HF. We did not have serial measurements of haemoglobin as well as haematocrit. We cannot exclude the possibility that some, or all, of the increase in haematocrit observed was due to reduction in plasma volume, although conventional diuretics generally do not increase haematocrit or haemoglobin.[18] Dapagliflozin improved survival compared with placebo, therefore there may be an element of survivor bias in the analysis where patients randomized to dapagliflozin were more likely to be alive, to be able to provide measurements of haematocrit and therefore experience correction of anaemia.

Conclusions

In conclusion, in patients with HFrEF in DAPA-HF, those with anaemia had worse outcomes. Dapagliflozin corrected anaemia more often than placebo and improved outcomes, irrespective of anaemia status at baseline.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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